

Pneumonia

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Work on pneumonia and the pneumococcus has continued to progress. The treatment of pneumococcal pneumonia by means of antipneumococcal rabbit serum, a therapeutic agent developed in the Hospital, yields excellent results. Despite the progress already made, much remains to be learned concerning many aspects of the problem. The results of Dr. Goebel's work on the production of an antiserum for pneumococci by the use of a synthetic antigen are very encouraging, and it is hoped that this work will open up a new approach to the production of certain therapeutic sera.

Preparation and use of a synthetic antigen in the production of antipneumococcal sera. For a number of years one of the major problems under investigation in the Hospital of The Rockefeller Institute has been a study of pneumococcus pneumonia, one of the most fatal of the acute infectious diseases in man. Methods were devised for studying the interaction of pneumococci and the tissue of the host, and the results were practically applied in the diagnosis and treatment of this disease long before the chemical nature of the substances involved were known.

In recent years the contributions of chemistry have added much to our understanding of the nature and specificity of these immunity reactions. As a result of these investigations it has been found that pneumococci are not all alike, but exhibit among themselves differences in biological specificity as diverse as though they were members of wholly unrelated species. Upon the basis of these differences pneumococci have been classified into thirty-two sharply defined and specific types. These researches have led to the development of curative sera, derived from the blood of immunized animals, which have been singularly successful in the

treatment of the disease in man.

That pneumococci are enveloped by a mucilaginous capsular substance which serves as a protective coating to the microorganisms permitting them to grow and multiply in the invaded host, has been known for many years. One of the most significant results of the chemo-immunological studies carried out in the Hospital has been the discovery that the differentiation of the various specific types of pneumococci is dependent upon chemical differences in their capsular substances. It has been revealed that each distinct type of pneumococcus builds about itself from the medium of its environment an encapsulating carbohydrate, the molecular architecture of which is in each instance different. Just as one may build an infinite variety of structures from the same building stones, so it is possible for each type of pneumococcus to construct an individual and characteristic capsular polysaccharide from the same atoms of carbon, hydrogen, and oxygen. The chemical approach to an understanding of the differentiation of the various pneumococcal types and their varied biological behavior resides in the comprehension of this fundamental difference in the chemical structure of the capsular carbohydrate peculiar to each specific type. For example, it has been found that the capsular polysaccharide of Type III Pneumococcus is a complex sugar which in many respects bears a striking relationship to cellulose, a substance universally distributed in nature. Cellulose is constituted from many molecules of the simple sugar glucose, which are combined to one another by means of a chemical linkage. On boiling with acid, cellulose may be broken down to the simple sugar glucose, or, if the hydrolysis is carried not quite so far, to a sugar made up of two glucose molecules. This latter sugar is called cellobiose. Now if the terminal, or twelfth carbon atom of

cellobiose is oxidized to an acidic group the sugar-acid "cellobiuronic acid" is obtained. It is this substance which constitutes the fundamental building stone of the complex capsular carbohydrate of the Type III Pneumococcus.

When the capsular polysaccharide of Type III Pneumococcus is isolated in pure form it is found to be devoid of certain immunological properties which it possessed in its native state in the capsule of the parent cell. No longer is it possible to induce in rabbits immunity to Type III pneumococcal infections by injection of the purified carbohydrate. But by chemical synthesis one may combine this single cellular constituent of the Type III Pneumococcus with a protein to yield an artificial substance, which when injected into rabbits is capable of inciting specific immunity to infection with virulent homologous organisms.

Cellobiuronic acid is found not only in the capsular polysaccharide of the Type III Pneumococcus, but it and other closely related sugar acids are present in the specific carbohydrates of other types of pneumococci and in other species of disease-producing bacteria as well. Because of this unusual distribution it was thought that cellobiuronic acid, a substance no more complex in chemical structure than common table sugar, might have an important immuno-chemical function. That this is so can be seen from the following account.

Unlike the immunologically active complex polysaccharide from which it is derived, the simple sugar cellobiuronic acid is devoid of any demonstrable serological activity. Yet by chemical synthesis it is possible to combine cellobiuronic acid with a protein to yield an artificial complex which when injected into rabbits renders these animals immune to infection with Type III pneumococci. Moreover the serum of these immune

rabbits when introduced into mice protects them against infection with living virulent pneumococci. In addition, the antiserum to this artificial antigen possesses the remarkable property of protecting mice against several other types of pneumococcal infections as well. The potency of the serum produced by the immunization of rabbits with this synthetic cellobiuronic acid antigen compares very favorably with the protective action of sera produced by standard methods employing the native bacteria from which this material is obtained.

Although the cellobiuronic acid used in the preparation of the artificially compounded antigen is derived from the products of hydrolysis of the specific polysaccharide of Type III *Pneumococcus*, there is no reason to believe that the same acid obtained from sources remote from bacteria would not serve equally well. The aldobionic acids, of which cellobiuronic acid is but one example, were discovered some years ago in the laboratories of the Hospital. They have since been found widely distributed throughout the plant kingdom. The direct chemical synthesis of two of these acids, gentobiuronic and acaciabiuronic acids, has already been achieved in Dr. Goebel's laboratory, and their use in artificially compounded antigens is at the present time under investigation.

Thus for the first time in the history of infectious diseases, it has been possible with an artificially compounded antigenic substance containing an aldobionic acid to produce a single serum which has proven effective in the treatment of more than one type of experimental pneumococcal infection. For those familiar with the field of chemical immunology it is apparent that this work may open a new and practical approach to the prevention and cure of pneumococcal infections in man.